Classical density functional theory to tackle solvation in molecular liquids

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Abstract

We present a brief review of the classical density functional theory of atomic and molecular fluids. We focus on the application of the theory to the determination of the solvation properties of arbitrary molecular solutes in arbitrary molecular solvent. This includes the prediction of the solvation free energies, as well as the characterization of the microscopic, three-dimensional solvent structure.

1 Introduction

The determination of the solvation free-energy of molecular solutes in molecular solvents is a problem of primary importance in physical chemistry and biology. From a theoretical point of view, two extreme strategies can be found in the literature. A standard route consists in using molecular simulation techniques such as molecular dynamics (MD) or Monte-Carlo (MC), with an explicit molecular solvent. There are a number of well-established statistical mechanics techniques to estimate absolute or relative free-energies by molecular simulations, for example thermodynamic integration methods based on umbrella sampling [1, 2], or generalized constraints [3]. In any case, the precise estimation of free-energies by computer simulation remains extremely costly; it requires to consider a sufficiently large number of solvent molecules around the molecular solute and, for this large system, to average a "generalized force" over many microscopic solvent configurations, and this for a lot of different points along the reversible thermodynamic integration path.

Another class of methods, known as implicit solvent models [4], relies on the assumption that the macroscopic laws remain valid at a microscopic level, and that solvation free energies can be computed by combining a dielectric continuum description of the solvent outside the solute core and a simple solvent-accessible surface area expression for the non-electrostatic contributions [5]. For

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the electrostatic part, the stationary Poisson-Boltzmann equation can be solved for the electrostatic potential using sharp definitions of the dielectric boundaries and various efficient numerical techniques, making it possible to handle very large biomolecular systems [6]. Density functional methods based on the minimization of polarization density [7] have been introduced too. There are serious limitations however to a continuum dielectric approach, and first of all the validity of the macroscopic electrostatic laws at microscopic distances, the neglect of the molecular nature of the solvent, and the ambiguous definition of all the non-electrostatic energetic contributions, such as hydrophobicity. Macroscopic approaches to hydrophobicity that mixes consistently with the Poisson-Boltzmann description are presently developed. [8, 9]

Beyond continuum descriptions, it is desirable however to devise and employ implicit solvent methods which (i) are able to cope with the molecular nature of the solvent, but without considering explicitly all its instantaneous microscopic degrees of freedom, and (ii) can provide solvation properties at a modest computer cost compared to explicit simulations. Such methods should rely on the theory of molecular liquids that has been developed in the second half of the last century and lie by now in classical textbooks [10–12]. Among possible approaches one should mention molecular integral equation theories in the reference interaction site (RISM) [13–16] or molecular [17–23], or mixed [24, 25] picture, Gaussian field theories [26, 27], the density functional theory (DFT) of molecular liquids [10, 28–39], or, finally, field theoretical approaches to dipolar solvent-ions mixtures, that lead to a generalization of the Poisson-Boltzmann equation accounting for particle size and dielectric saturation [40–44]. Note that, close to our purpose, a 3D-version of the RISM equations has been developed recently to describe the solvation of objects of complex shape [45–50].

Our focus here is classical density functional theory (DFT), and eventually a molecular version of it that we will call Molecular Density Functional Theory (MDFT). The basic theoretical principles of classical DFT can be found in the seminal paper by B. Evans [28] and subsequent excellent reviews by him [28–30] and other authors [51]. The advent in the late 1980's of a quasi-exact DFT for inhomogeneous hard sphere mixtures, the fundamental measure theory [52–57], has promoted recently a great deal of applications to atomic-like fluids in bulk or confined conditions or at interfaces. Classical "atomic" DFT can be considered nowadays as a method of choice for many chemical engineering problems [58, 59]. Much less applications exist for molecular fluids, for which solvent orientations should be considered. The description has been generally limited to generic dipolar solvents [60, 61] or dipolar solvent/ions mixtures [33–36]; such approach may be considered already as "civilized" compared to primitive continuum models [35]. We have proposed recently an extension of MDFT to arbitrary fluid/solvents in the precise goal of describing the solvation of three-dimensional molecular object in arbitrary solvents. [37–39, 62–70] A RISM-based DFT approach of molecular solvation has been developed recently too [71].

The outline of the present review is as follows. We first recall the basic principles of cDFT for atomic-like fluids. We then describe the particular but

fundamental case of the hard-sphere fluid, and the associated fundamental measure theory (FMT), focusing on a "scalar" formulation due to Kierlik and Rosinberg [53, 54], instead of the standard "vectorial" version introduced initially by Rosenfeld [52]. We then turn to Lennard-Jones fluids, for which the HS fluid can be used as a reference in various ways to construct a functional. The last section will be devoted to molecular solvent, modeled by rigid polyatomic molecules with an orientation. The discussion will focus on a model dipolar solvent, the Stockmayer fluid, and then extend to realistic models of polar liquids such as acetonitrile and water.

2 The case of atomic fluids

2.1 General formulation

In this section we begin with recalling the basis of the density functional theory of liquids, and discussing the general problem of a molecular solvent submitted to an external field. In the applications we have in mind, the external field will be created by a molecular solute of arbitrary shape dissolved at infinite dilution in the solvent. The individual solvent molecules will be considered later as rigid bodies described by their position $\mathbf{r}$ and orientation ω. In this section we restrict the discussion to atomic or pseudo-atomic solvents (such as CCl_4) modeled by spherical particles for which only the position $\mathbf{r}$ matters.

The grand potential density functional for a fluid having an inhomogeneous density $\rho(\mathbf{r})$ in the presence of an external field $V_{ext}(\mathbf{r})$ can be defined as [28, 29],

$$\Omega[\rho] = F[\rho] - \mu_s \int \rho(\mathbf{r}) d\mathbf{r}, \tag{1}$$

where $F[\rho]$ is the Helmholtz free energy functional and μ_s is the chemical potential. The grand potential can be evaluated relatively to a reference homogeneous fluid having the same chemical potential μ_s and particle density ρ_0

$$\Omega[\rho] = \Omega[\rho_0] + \mathcal{F}[\rho]. \tag{2}$$

Following the general theoretical scheme introduced by Evans [10, 28, 29, 72], the density functional $\mathcal{F}[\rho]$ can be split into three contributions: an ideal term, an external potential term and an excess free-energy term accounting for the intrinsic interactions within the fluid,

$$\mathcal{F}[\rho] = \mathcal{F}_{id}[\rho] + \mathcal{F}_{ext}[\rho] + \mathcal{F}_{exc}[\rho], \tag{3}$$

with the following expressions of the first two terms

$$\mathcal{F}_{id}[\rho] = k_B T \int d\mathbf{r}_1 \left[\rho(\mathbf{r}_1) \ln \left(\frac{\rho(\mathbf{r}_1)}{\rho_0} \right) - \rho(\mathbf{r}_1) + \rho_0 \right], \tag{4}$$

$$\mathcal{F}_{ext}[\rho] = \int d\mathbf{r}_1 \, V_{ext}(\mathbf{r}_1) \rho(\mathbf{r}_1). \tag{5}$$

3

There are several ways to arrive to an exact expression of the excess free-energy, i.e. using an adiabatic perturbation of the pair potential (the so-called adiabatic connection route in electronic DFT), of the external potential, or of the density itself. If the latest route is chosen, one can define $\mathcal{F}_{exc}[\rho]$ as: [28]

$$\mathcal{F}_{exc}[\rho] = k_B T \iint d\mathbf{r}_1 d\mathbf{r}_2 \, C(\mathbf{r}_1, \mathbf{r}_2) \, \Delta\rho(\mathbf{r}_1)\Delta\rho(\mathbf{r}_2), \tag{6}$$

with $\Delta\rho(\mathbf{r}) = \rho(\mathbf{r}) - \rho_0$. The function $C(\mathbf{r}_1, \mathbf{r}_2)$ is still a functional of $\rho(\mathbf{r})$ defined by

$$C(\mathbf{r}_1, \mathbf{r}_2) = \int_0^1 d\alpha \, (\alpha - 1) \, c^{(2)}(\mathbf{r}_1, \mathbf{r}_2; [\rho_\alpha]), \tag{7}$$

where $c^{(2)}(\mathbf{r}_1, \mathbf{r}_2; [\rho_\alpha])$ is the two particle direct correlation function, i.e. by definition the second order derivative of the excess free-energy with respect to density, evaluated at the intermediate density $\rho_\alpha(\mathbf{r}) = \rho_0 + \alpha\Delta\rho(\mathbf{r})$. Eqs 6-7 follows naturally when expressing the functional from the knowledge of its second-derivatives [28].

The equilibrium condition reads

$$\left.\frac{\delta\Omega[\rho]}{\delta\rho}\right|_{\rho=\rho_{eq}} = 0 \qquad \Longrightarrow \qquad \left.\frac{\delta\mathcal{F}[\rho]}{\delta\rho}\right|_{\rho=\rho_{eq}} = 0. \tag{8}$$

When minimizing the density functional $\mathcal{F}[\rho]$ with respect to $\rho(\mathbf{r})$, the value at the minimum is the difference of the solvent grand potential with and without the solute, and thus the solute solvation free-energy. The associated density $\rho_{eq}(\mathbf{r})$ is the equilibrium inhomogeneous density.

The functional defined by eqs 3-6 is formally exact but the inhomogeneous direct correlation functions entering the definition of the excess term are indeed unknown. However, simple approximations can be proposed for this quantity. The most natural one consists in expanding the inhomogeneous direct correlation function $c^{(2)}(\mathbf{r}_1, \mathbf{r}_2; [\rho_\alpha])$ around $\alpha = 0$, that is, around the homogeneous density ρ_0:

$$c^{(2)}(\mathbf{r}_1, \mathbf{r}_2; [\rho_\alpha]) = c^{(2)}(\mathbf{r}_1, \mathbf{r}_2; [\rho_0]) + \alpha \int d\mathbf{r}_3 \, c^{(3)}(\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3; [\rho_0]) \, \Delta\rho(\mathbf{r}_3) + \dots \tag{9}$$

Such expression involves the two, three, n-particle direct correlation functions of the homogeneous fluid [10]. The first term is the (two-body) direct correlation function (DCF) of the homogeneous solvent, that depends on $r_{12} = |\mathbf{r}_2 - \mathbf{r}_1|$, and can be thus denoted as $c_S(r_{12}; \rho_0)$ (S for spherical component, preparing ourselves to non-spherical solvents).

Using eq. 7, the excess term can thus be written as

$$\mathcal{F}_{exc}[\rho] = -\frac{\beta^{-1}}{2}\int d\mathbf{r}_1 d\mathbf{r}_2 \, c_S(r_{12}; \rho_0) \, \Delta\rho(\mathbf{r}_1)\Delta\rho(\mathbf{r}_2) + \mathcal{F}_B[\rho], \tag{10}$$

where we have defined the bridge functional

$$\mathcal{F}_B[\rho] = -\frac{1}{6}\int d\mathbf{r}_1 d\mathbf{r}_2 d\mathbf{r}_3 \, c^{(3)}(\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3; [\rho_0]) \, \Delta\rho(\mathbf{r}_1)\,\Delta\rho(\mathbf{r}_2)\,\Delta\rho(\mathbf{r}_3) + o(\Delta\rho^4), \tag{11}$$

4

which thus starts with a cubic term in $\Delta\rho$. Setting $\mathcal{F}_B[\rho] = 0$ correspond to the so-called homogeneous reference fluid (HRF) approximation. It can be shown to be equivalent to the hypernetted chain (HNC) approximation in integral equation theories [30]. The input of the theory is the direct correlation function of the pure solvent, which can be extracted from simulation or experimental data by measuring the total correlation function $h_S(r) = g(r) - 1$ and solving subsequently the Ornstein-Zernike equation, i.e. in Fourier space:

$$1 - \rho_0 c_S(k) = (1 + \rho_0 h_S(k))^{-1} = \chi_n^{-1}(k). \tag{12}$$

$\chi_n(r)$ is the structure factor, or the density susceptibility, measuring density-density correlations at a given distance in the fluid. The excess free energy can thus be expressed also in terms of the susceptibility

$$\mathcal{F}_{exc}[\rho] = \frac{k_B T}{2} \int d\mathbf{r}_1 d\mathbf{r}_2 \, \chi_n^{-1}(r_{12}) \, \Delta\rho(\mathbf{r}_1)\Delta\rho(\mathbf{r}_2) - \frac{k_B T}{2\rho_0} \int d\mathbf{r} \, \Delta\rho(\mathbf{r})^2 + \mathcal{F}_B[\rho]. \tag{13}$$

2.2 Fundamental Measure Theory for the hard-sphere fluid: Scalar versus Vectorial Formulation

We focus here on the particular case of the hard-sphere fluid and describe briefly the fundamental measure theory (FMT) introduced by Rosenfeld [52] and Kierlik and Rosinberg [53]. Although the theory is valid for arbitrary hard-sphere mixtures, we consider a one-component HS fluid composed of hard spheres of radius R and at a bulk density ρ_0. The fluid is subjected to an external perturbation, for example a solid interface or a molecular solute of arbitrary shape embedded in the fluid, that creates a position-dependent external potential $V_{ext}(\mathbf{r})$ and thus an inhomogeneous density $\rho(\mathbf{r})$. The excess functional of eq. 6 can be written as

$$\mathcal{F}_{exc}[\rho] = F_{exc}^{HS}[\rho] - F_{exc}^{HS}[\rho_0] - \mu_{exc}^{HS} \int d\mathbf{r} \left(\rho(\mathbf{r}) - \rho_0 \right), \tag{14}$$

where $F_{exc}^{HS}(\rho)$ is the excess Helmholtz free-energy functional for the hard-sphere fluid and μ_{exc}^{HS} is the bulk excess chemical potential defined by

$$\mu_{exc}^{HS} = \frac{\delta \mathcal{F}_{exc}^{HS}[\rho]}{\delta\rho}|_{\rho=\rho_0}, \tag{15}$$

so that obviously $\frac{\delta \mathcal{F}_{exc}[\rho]}{\delta\rho}|_{\rho=\rho_0} = 0$. In the FMT introduced by Rosenfeld [52], the excess functional for the hard-sphere fluid can be written in terms of a set of N_w weighted densities, $n_\alpha(\mathbf{r})$:

$$\mathcal{F}_{exc}[\{\rho_i(\mathbf{r})\}] = k_B T \int d\mathbf{r} \, \Phi(\{n_\alpha(\mathbf{r})\}) \tag{16}$$

with

$$n_\alpha(\mathbf{r}) = \int d\mathbf{r}' \, \rho(\mathbf{r}') \, \omega_\alpha(\mathbf{r} - \mathbf{r}') = \rho(\mathbf{r}) \star \omega_\alpha(\mathbf{r}), \tag{17}$$

where $\omega_\alpha(\mathbf{r})$ are geometrical weight functions to be defined below and $\star$ indicates the convolution of the microscopic densities by those weight functions.

In the original Rosenfeld's derivation there are four scalar weight functions, $\omega_\alpha^i(\mathbf{r}), \alpha = 0, 1, 2, 3$, and two vectorial ones $\vec{\omega}_1(\mathbf{r}), \vec{\omega}_2(\mathbf{r})$ that are defined by

$$\omega_3(\mathbf{r}) = \Theta(R - r) \tag{18}$$

$$\omega_2(\mathbf{r}) = 4\pi R \omega_1(\mathbf{r}) = 4\pi R^2 \omega_0(\mathbf{r}) = \delta(R - r) \tag{19}$$

$$\vec{\omega}_2(\mathbf{r}) = 4\pi R \vec{\omega}_1(\mathbf{r}) = \frac{\mathbf{r}}{r} \delta(R - r). \tag{20}$$

$\Theta(r)$ denotes the Heaviside function and $\delta(r)$ the Dirac distribution. The excess free-energy density Φ derived by Rosenfeld for Eq. 16 is a function of the four position-dependent weighted densities, $n_\alpha(\mathbf{r}), \alpha = 0, 1, 2, 3$, and of the two vectorial ones, $\vec{n}_1(\mathbf{r}), \vec{n}_2(\mathbf{r})$, which generates in the homogeneous limit the Percus-Yevick equation of state for hard-sphere mixtures. Starting from the generalization of the Carnahan-Starling (CS) equation of state to mixtures (namely the Mansoori-Carnahan-Starling-Leland equation (MCSL)) instead of PY, Roth et al [55] and Wu et al [56] were later able to obtain a modified expression based on the same definition of the weighted densities (either called white-bear (WB) version or modified FMT version (MFMT)). This modified version of FMT takes advantage of the fact that the CS expression provides one a better equation of state that PY.

Ten years before those latest developments, Kierlick and Rosinberg were able to derive an alternative version of FMT which involves only four scalar weight functions $\omega_\alpha(\mathbf{r}), \alpha = 0, 1, 2, 3$. [53, 54]. The last two weights are identical to Eq. 18-19, whereas the first two ones are given by

$$\omega_1(\mathbf{r}) = \frac{1}{8\pi} \delta'(R - r) \tag{21}$$

$$\omega_0(\mathbf{r}) = \frac{1}{8\pi} \delta''(R - r) + \frac{1}{2\pi r} \delta'(R - r) \tag{22}$$

Those weight functions appear naturally in the derivation as the inverse Fourier transforms of

$$\omega_3(k) = \frac{4\pi}{k^3}(\sin(kR) - kR\cos(kR))$$

$$\omega_2(k) = \frac{4\pi R}{k} \sin(kR_i)$$

$$\omega_1(k) = \frac{1}{2k}(\sin(kR) + kR\cos(k)) \tag{23}$$

$$\omega_0(k) = \cos(kR) + \frac{kR}{2}\sin(kR).$$

Although the main part of the papers by Kierlik and Rosinberg relies on a PY expression for the excess free energy density

$$\Phi^{PY}[n_\alpha] = -n_0 \ln(1 - n_3) + \frac{n_1 n_2}{1 - n_3} + \frac{1}{24\pi} \frac{n_2^3}{(1 - n_3)^2}, \tag{24}$$

the authors do mention in their conclusion that a CS (more precisely MCSL) expression could be used instead

$$\Phi^{CS}[n_\alpha] = \left(\frac{1}{36\pi} \frac{n_2^3}{n_3^2} - n_0 \right) \ln(1 - n_3) + \frac{n_1 n_2}{1 - n_3} + \frac{1}{36\pi} \frac{n_2^3}{(1 - n_3)^2 n_3}. \qquad (25)$$

They point out the fact that this expression is more precise than the PY one, but using it while keeping the expression of the weights unchanged leads to thermodynamic inconsistencies; those inconsistencies are indeed present in the WB or MFMT formulations too. There is clearly a trade off to be made between precision and theoretical consistency. It was later shown by Phan et al. that the Kierlik and Rosinberg's approach is mathematically equivalent to the original vectorial version. [73] On a practical point of view, however, and especially in the perspective of 3D applications, the KR formulation is advantageous with respect to the Rosenfeld's formulation since the number of *independent* weighted densities is reduced from 5 to 4 for the one component system, and from $(10 + N_s)$ to $(4 + N_s)$ for a mixture of N_s components, with $N_s \geq 2$; thus from 12 to 6 for a binary mixture. An efficient numerical implementation in three-dimensions of the Kierlik-Rosinberg FMT functional is detailed in Ref. [65]. The numerical efficiency of the algorithms, in terms of convergence rate and system size dependency, is briefly illustrated in Fig. 1.

2.3 The Lennard-Jones fluid

Building the thermodynamics of the Lennard-Jones fluid by taking the suitable hard-sphere fluid as a reference and building in the attractive interaction as a perturbation is indeed a classics in liquid state theory and is at the basis of the Van der Waals theory of fluids. When coming to functionals, this idea can be declined in several variants, the most natural one being to use a FMT functional for the repulsive part and a mean-field approximation (or mean spherical approximation, MSA) for the attractive part [30]. Along the lines given above, another route is to approximate the bridge functional in eq. 10 by a hard sphere bridge functional, introduced by Rosenfeld as a universal bridge function [74,75]

$$\begin{aligned} \mathcal{F}[\rho(\mathbf{r})] &= k_B T \int d\mathbf{r} \left[\rho(\mathbf{r}) \ln \left(\frac{\rho(\mathbf{r})}{\rho_0} \right) - \rho(\mathbf{r}) + \rho_0 \right] + \int d\mathbf{r}\, V_{ext}(\mathbf{r})\rho(\mathbf{r}) \\ &- \frac{k_B T}{2} \int d\mathbf{r}_1 d\mathbf{r}_2\, c_S(r_{12}; \rho_0)\Delta\rho(\mathbf{r}_1)\,\Delta\rho(\mathbf{r}_2) + \mathcal{F}_B^{HS}[\rho], \qquad (26) \end{aligned}$$

where

$$\begin{aligned} \mathcal{F}_B^{HS}[\rho(\mathbf{r})] &= F_{exc}^{HS}[\rho(\mathbf{r})] - F_{exc}^{HS}[\rho_0] - \mu_{exc}^{HS} \int d\mathbf{r}\Delta\rho(\mathbf{r}) \\ &+ \frac{k_B T}{2} \int d\mathbf{r}_1 d\mathbf{r}_2\, c_S^{HS}(r_{12}; \rho_0)\Delta\rho(\mathbf{r}_1)\,\Delta\rho(\mathbf{r}_2). \qquad (27) \end{aligned}$$

The first three terms represent the one-component hard-sphere KR-FMT excess functional defined in the previous section and the associated chemical potential
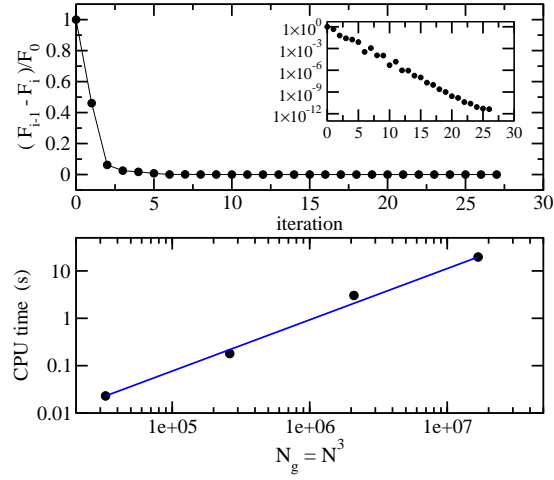
Figure 1: Top: Typical plot of the free energy difference between two successive steps (normalized by the initial energy) versus minimization-step number (Here a benzene molecule in a one-component HS reference fluid modeling SPC water). The inlet represents the same with a logarithmic scale in ordinates. Bottom: CPU time per minimization step versus number of 3D-grid points. The circle correspond in increasing order to N= 32, 64, 128, and 256.

yielding equilibrium at $\rho(\mathbf{r}) = \rho_0$. The fourth term involves the direct correlation function of the HS fluid at the same density, i.e

$$c_S^{HS}(|\mathbf{r}_1 - \mathbf{r}_2|; \rho_0) = -\frac{\delta^2 \mathcal{F}_{exc}^{HS}[\rho]}{\delta\rho(\mathbf{r}_1)\delta\rho(\mathbf{r}_2)}|_{\rho(\mathbf{r})=\rho_0}. \tag{28}$$

This function can be easily obtained in Fourier space as

$$c_S^{HS}(k; \rho_0) = -\sum_{\alpha,\beta} \frac{\partial^2 \Phi}{\partial n_\alpha \partial n_\beta}(\{n_\gamma^0\})\, \omega_\alpha(k)\omega_\beta(k), \tag{29}$$

where $\{n_\gamma^0\}$ represent the weighted densities for a uniform fluid of density ρ_0 and the $\omega_{\alpha,\beta}(k)$ are the weights of eq. 23. The second derivatives have to be taken for the PY or CS functions of eqs 24 or 25. Note that defined as in eq. 27, $\mathcal{F}_B^{HB}[\rho(\mathbf{r})]$ carries an expansion in $\Delta\rho$ of order 3 and higher that corrects the second order expansion of the excess free energy in eq. 26. The excess functional can also be re-expressed as

$$
\begin{aligned}
\mathcal{F}_{exc}[\rho] &= F_{exc}^{HS}[\rho] - F_{exc}^{HS}[\rho_0] - \mu_{exc}^{HS}\int d\mathbf{r}\Delta\rho(\mathbf{r}) \\
&\quad - \frac{k_B T}{2}\int d\mathbf{r}_1 d\mathbf{r}_2\, c_S^{att}(r_{12}; \rho_0)\, \Delta\rho(\mathbf{r}_1)\Delta\rho(\mathbf{r}_2),
\end{aligned} \tag{30}
$$

where we have defined the "attractive" DCF by

$$c_S^{att}(r_{12}; \rho_0) = c_S(r_{12}; \rho_0) - c_S^{HS}(r_{12}; \rho_0). \tag{31}$$

Eq. 30 is the basis of the first order mean-spherical approximation (FMSA) theory developed by Tang [76].

We show here how this FMSA theory works for our purpose: the prediction of solvation properties of dissolved molecular objects. In Fig. 2.3, we compare the solvation free energy of a LJ sphere of increasing diameter in a LJ fluid with $\rho^* = 0.85, T^* = 0.88$, as computed by Monte-Carlo simulations by Lazaridis [77], to the results obtained by DFT minimization with different HS diameters, d. It can be seen that the results are extremely sensitive to the choice of d, and that the best agreement is obtained for $d = 1.014\sigma$ (indeed close to 1, that would be the initial guess value). For that value, we have plotted in Fig. 2.3 the microscopic solvent density, $g(r) = \rho(r)/\rho_0$, obtained for solute of different sizes by direct simulation, or by DFT in the HNC or FMSA approximation. It can be seen that the addition of hard-sphere bridge in FMSA greatly improve the results compared to the HRF (or HNC) approximation and yields a correct structure.
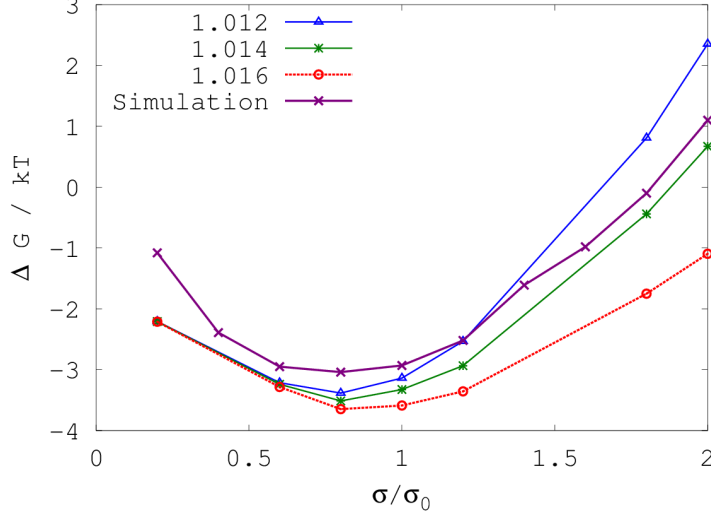
Figure 2: Solvation free-energy obtained by DFT using the HS bridge functional of 27 with different HS diameters, compared to the Monte-Carlo results of Lazaridis [77].

3 The case of molecular fluids: Molecular density functional theory (MDFT)

3.1 General formulation

The solvent molecules now carry a molecular structure that is described by a collection of distributed atomic interaction sites. The theory is formulated in the molecular picture in which each solvent molecule is considered as a rigid body and characterized by its position, $\mathbf{r}$ (e.g. the position of center of mass), and by its orientation, ω, defined by the three Euler angles $\omega = (\theta, \phi, \psi)$. Thus, in the presence of an external perturbation, the solvent is now characterized by an inhomogeneous position and orientation density $\rho(\mathbf{r}, \omega)$. The solute, as the solvent, is described in microscopic details by a molecular non-polarizable "force-field" involving atomic Lennard-Jones and partial charges parameters. Given that the solute is fixed and defined by the position, $\mathbf{R}_i$, of its different atomic sites, the external potential is defined by

$$V_{ext}(\mathbf{r}, \omega) = \sum_{i \in solute} \sum_{j \in solvent} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}, \qquad (32)$$

where ϵ_{ij} and σ_{ij} are the Lennard-Jones parameters between solute site i and solvent site j, and q_i and q_j are the partial charges carried by those sites.
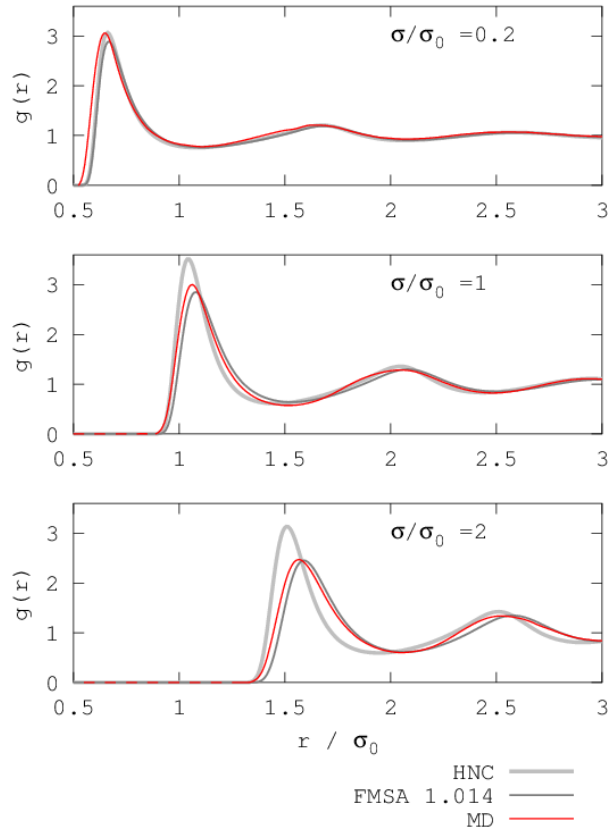
Figure 3: Reduced solvent density around LJ solutes of different diameters, using the HNC approximation, or adding a hard-sphere bridge functional with $d = 1.014\sigma$.

11

The relative site-site vectors are function of the solvent molecule position and orientation and defined as $\mathbf{r}_{ij} = \mathbf{r} + \mathbf{R}(\omega)\mathbf{s}_j - \mathbf{R}_i$, where $\mathbf{s}_j$ denotes the site positions in the molecular frame and $\mathbf{R}(\omega)$ is the rotation matrix associated to ω.

The same density functional as in eqs 1-3 can be written for $\rho(\mathbf{r}, \omega)$, with an ideal, external, and excess part:

$$
\begin{aligned}
\mathcal{F}_{id}[\rho] &= k_B T \int d\mathbf{r} d\omega \left[\rho(\mathbf{r}, \omega))\ln\left(\frac{8\pi^2 \rho(\mathbf{r}, \omega)}{n_0}\right) - \rho(\mathbf{r}, \omega)) + \frac{n_0}{8\pi^2} \right] \\
\mathcal{F}_{ext}[\rho] &= \int d\mathbf{r} d\omega \, V_{ext}(\mathbf{r}, \omega)\rho(\mathbf{r}, \omega) \qquad\qquad (33) \\
\mathcal{F}_{exc}[\rho] &= -\frac{1}{2} k_B T \iint d\mathbf{r}_1 d\mathbf{r}_2 d\omega_1 d\omega_2 \Delta\rho(\mathbf{r}_1, \omega_1) \, c(\mathbf{r}_1 - \mathbf{r}_2, \omega_1, \omega_2') \, \Delta\rho(\mathbf{r}_2, \omega_2) \\
&\quad + \mathcal{F}_B[\rho(\mathbf{r}, \omega)],
\end{aligned}
$$

where $\Delta\rho(\mathbf{r}, \omega) = \rho(\mathbf{r}, \omega) - n_0/8\pi^2$, n_0 being the particle number density of the reference bulk fluid. The first term represents the Homogeneous Reference Fluid approximation (or HNC approximation) where the excess free-energy density is written in terms of the angular-dependent direct correlation of the *pure* solvent. The second term represents the unknown correction to that term (or Bridge functional) that, again, can be expressed as of a systematic expansion of the solvent correlations in terms of the three-body, .. n-body terms direct correlation functions.

3.2 The Stockmayer solvent

To test and illustrate the theory, we start from the simplest conceivable model of dipolar solvent, the Stockmayer model, characterized by a single Lennard-Jones center with parameters σ_s, ϵ_s and a dipole $\boldsymbol{\mu}_s = p\boldsymbol{\omega}$, where $\boldsymbol{\omega}$ is the unitary orientational vector of the molecule –which here replaces the orientation noted ω above. The parameters are selected to make the model look like water (similar density, $n_0 = 0.033$ particles$/^3$, particle size, $\sigma_s = 3$, and molecular dipole, $p = 1.85D$) although not tasting quite as water (no hydrogen bond in the model!). For such model, the external potential can be written as

$$
V_{ext}(\mathbf{r}, \boldsymbol{\omega}) = \Phi_{LJ}(\mathbf{r}) - \mu \mathbf{E}_q(\mathbf{r}) \cdot \boldsymbol{\omega} \qquad\qquad (34)
$$

with

$$
\begin{aligned}
\Phi_{LJ}(\mathbf{r}) &= \sum_{i=1}^{M} 4\epsilon_{si} \left[\left(\frac{\sigma_{si}}{|\mathbf{r} - \mathbf{R}_i|}\right)^{12} - \left(\frac{\sigma_{si}}{|\mathbf{r} - \mathbf{R}_i|}\right)^{6} \right] \qquad\qquad (35) \\
\mathbf{E}_q(\mathbf{r}) &= \frac{1}{4\pi\epsilon_0} \sum_{i=1}^{M} \frac{q_i(\mathbf{r} - \mathbf{R}_i)}{|\mathbf{r} - \mathbf{R}_i|^3}. \qquad\qquad (36)
\end{aligned}
$$

It is also argued in Refs [17, 19] that the c-functions can be expanded onto a rotational invariants basis set keeping, to a good approximation approximation,

the same order as the intermolecular potential, namely

$$c(\mathbf{r}_{12}, \boldsymbol{\omega}_1, \boldsymbol{\omega}_2) \quad = \quad c_S(r_{12}) + c_\Delta(r_{12})\, \Phi^{110}(\boldsymbol{\omega}_1, \boldsymbol{\omega}_2) + c_D(r_{12})\, \Phi^{112}(\boldsymbol{\omega}_1, \boldsymbol{\omega}_2) \quad (37)$$

where

$$\begin{aligned}
\Phi^{110} &= \boldsymbol{\omega}_1 \cdot \boldsymbol{\omega}_2, \\
\Phi^{112} &= 3\,(\boldsymbol{\omega}_1 \cdot \hat{\mathbf{r}}_{12})\,(\boldsymbol{\omega}_2 \cdot \hat{\mathbf{r}}_{12}) - \boldsymbol{\omega}_1 \cdot \boldsymbol{\omega}_2
\end{aligned} \qquad (38)$$

represents the two first non-isotropic spherical invariants. The three components c_S, c_Δ, c_D of $c(\mathbf{r}_{12}, \boldsymbol{\omega}_1, \boldsymbol{\omega}_2)$ can be obtained from the the corresponding components of the total correlation function, $h(\mathbf{r}_{12}, \boldsymbol{\omega}_1, \boldsymbol{\omega}_2)$, by inversion of the angular-dependent OZ equation. The total correlation function itself can be measured by using, e.g., MD simulations. We have used here the original Wertheim's notations with subscripts S, Δ, and D for the different h- and c-components. In this approximation, it was shown in Refs [37, 39] that the OZ equation can be solved directly for the different components in real space. Results of equivalent precision can be reached from inversion relations in k-space [78].

Defining the number density,

$$n(\mathbf{r}) = \int d\boldsymbol{\omega}\, \rho(\mathbf{r}, \boldsymbol{\omega}), \qquad (39)$$

and the polarization density,

$$\mathbf{P}(\mathbf{r}) = \mu \int d\boldsymbol{\omega}\, \boldsymbol{\omega}\, \rho(\mathbf{r}, \boldsymbol{\omega}), \qquad (40)$$

and injecting the expression 37 of $c(\mathbf{r}_{12}, \boldsymbol{\omega}_1, \boldsymbol{\omega}_2)$ into the functional of eq. 33, it can be shown that external and excess terms can be written as functionals of $n(\mathbf{r})$ and $\mathbf{P}(\mathbf{r})$ instead of the much more complex variable $\rho(\mathbf{r}, \boldsymbol{\omega})$, namely

$$\begin{aligned}
\mathcal{F}_{ext}[n, \mathbf{P}] &= \int d\mathbf{r}\, \Phi_{LJ}(\mathbf{r}) - \int d\mathbf{r}\, \mathbf{P}(\mathbf{r}) \cdot \mathbf{E}_q(\mathbf{r}) \\
\mathcal{F}_{exc}[n, \mathbf{P}] &= -\frac{k_B T}{2} \int d\mathbf{r}_1 d\mathbf{r}_2\, c_S(r_{12}) \Delta n(\mathbf{r}_1) \cdot \Delta n(\mathbf{r}_1) - \frac{k_B T}{2\mu^2} \int d\mathbf{r}_1 d\mathbf{r}_2\, c_\Delta(r_{12}) \mathbf{P}(\mathbf{r}_1) \cdot \mathbf{P}(\mathbf{r}_1) \\
&\quad - \frac{k_B T}{2\mu^2} \int d\mathbf{r}_1 d\mathbf{r}_2\, c_D(r_{12}) \left[3(\mathbf{P}(\mathbf{r}_1) \cdot \hat{\mathbf{r}}_{12})(\mathbf{P}(\mathbf{r}_2) \cdot \hat{\mathbf{r}}_{12}) - \mathbf{P}(\mathbf{r}_1) \cdot \mathbf{P}(\mathbf{r}_1) \right]. \qquad (41)
\end{aligned}$$

At this stage, the expression of the ideal term can be kept unchanged as a function of $\rho(\mathbf{r}, \omega)$ as in eq. 33 and the minimization of the whole functional still performed with respect to $\rho(\mathbf{r}, \omega)$. The above expressions of the nonlocal excess free energy requires to perform FFT's for $n(\mathbf{r}), \mathbf{P}(\mathbf{r})$ rather than for $\rho(\mathbf{r}, \omega)$ and this reduces considerably the computation time. We can go even a little bit further, and show that the ideal part itself can be expressed as a functional of

13

$n(\mathbf{r})$ and $\mathbf{P}(\mathbf{r})$ [37], namely

$$
\mathcal{F}_{id}[n, \mathbf{P}] \quad = \quad k_B T \int d\mathbf{r}\, n(\mathbf{r}) \ln(\frac{n(\mathbf{r})}{n_0}) - n(\mathbf{r}) + n_0 \tag{42}
$$

$$
+ \quad k_B T \int d\mathbf{r}\, n(\mathbf{r}) \left(\ln \left[\frac{\mathcal{L}^{-1}(\frac{P(\mathbf{r})}{\mu\, n(\mathbf{r})})}{\sinh(\mathcal{L}^{-1}(\frac{P(\mathbf{r})}{\mu\, n(\mathbf{r})}))} \right] + \frac{P(\mathbf{r})}{\mu\, n(\mathbf{r})}\, \mathcal{L}^{-1}(\frac{P(\mathbf{r})}{\mu\, n(\mathbf{r})}) \right) .
$$

In the second, polarization term, $\mathcal{L}$ designates the Langevin function and $\mathcal{L}^{-1}$ its inverse; $P(\mathbf{r})$ is the modulus of the polarization vector $\mathbf{P}(\mathbf{r})$. The linearization of this term for small polarization fields yields the correct electrostatic limit, namely

$$
\mathcal{F}_{id}[n, \mathbf{P}] = \int d\mathbf{r}\, \frac{\mathbf{P}(\mathbf{r})^2}{2\alpha_d n(\mathbf{r})}, \tag{43}
$$

where $\alpha_d = \mu^2/3k_B T$ is the usual equivalent polarizability of a dipole μ at the temperature T. One recognizes the expression of the polarization free-energy in a medium with local electric susceptibility $\chi_e(\mathbf{r}) = \alpha_d n(\mathbf{r})$.

Although the functional is now complete and usable as such, we proceed by looking at an equivalent of eq. 41 involving susceptibilities rather than direct correlation functions. We introduce the longitudinal and transverse polarization in k-space

$$
\begin{aligned}
\mathbf{P}_L(\mathbf{k}) &= (\mathbf{P}(\mathbf{k}) \cdot \hat{\mathbf{k}})\, \hat{\mathbf{k}} \\
\mathbf{P}_T(\mathbf{k}) &= \mathbf{P}(\mathbf{k}) - \mathbf{P}_L(\mathbf{k}),
\end{aligned} \tag{44}
$$

where $\hat{\mathbf{k}} = \mathbf{k}/k$. The electrostatic part of the excess free energy in eq.41 can be written in k-space

$$
\begin{aligned}
\mathcal{F}_{exc}^{elec} &= \quad -\frac{1}{2}\frac{k_B T}{\mu^2} \int d\mathbf{k}\, c_\Delta(k)\, \mathbf{P}(\mathbf{k}) \cdot \mathbf{P}(-\mathbf{k}) \\
&\quad - \frac{1}{2}\frac{k_B T}{\mu^2} \int d\mathbf{k}\, c_D(k) \left[3(\mathbf{P}(\mathbf{k}) \cdot \hat{\mathbf{k}})(\mathbf{P}(-\mathbf{k}) \cdot \hat{\mathbf{k}}) - \mathbf{P}(\mathbf{k}) \cdot \mathbf{P}(-\mathbf{k}) \right]
\end{aligned} \tag{45}
$$

This can be easily rearranged into

$$
\mathcal{F}_{exc}^{elec} = -\frac{1}{2}\frac{k_B T}{\mu^2} \left[\int d\mathbf{k}\, c_-(k)\, \mathbf{P}_T(\mathbf{k}) \cdot \mathbf{P}_T(-\mathbf{k}) + \int d\mathbf{k}\, c_+(k)\, \mathbf{P}_L(\mathbf{k}) \cdot \mathbf{P}_L(-\mathbf{k}) \right] \tag{46}
$$

with the usual definitions [10, 79, 80]:

$$
\begin{aligned}
c_-(k) &= c_\Delta(k) - c_D(k) \\
c_+(k) &= c_\Delta(k) + 2c_D(k).
\end{aligned} \tag{47}
$$
$$
\tag{48}
$$

We use now the relations between $c_-(k)$ and $c_+(k)$ and the longitudinal and transverse dielectric constant $\epsilon_L(k)$ and $\epsilon_T(k)$, or, alternatively, the longitudinal

and transverse dielectric susceptibilities $\chi_L(k)$ and $\chi_T(k)$ (see Refs [10, 79–82])

$$1 - \frac{n_0}{3}c_+(k) = \frac{3y}{1 - 1/\epsilon_L(k)} = \frac{3y}{4\pi\chi_L(k)}, \tag{49}$$

$$1 - \frac{n_0}{3}c_-(k) = \frac{3y}{\epsilon_T(k) - 1} = \frac{3y}{4\pi\chi_T(k)}, \tag{50}$$

with $y = \mu^2 n_0/9k_BT\epsilon_0$, such that

$$\begin{aligned} F_{exc}^{elec} &= -\frac{3k_BT}{n_0\mu^2}\int d\mathbf{k}\,\mathbf{P}(\mathbf{k})\cdot\mathbf{P}(-\mathbf{k}) \\ &+ \frac{1}{8\pi\epsilon_0}\left[\int d\mathbf{k}\,\frac{\mathbf{P}_T(\mathbf{k})\cdot\mathbf{P}_T(-\mathbf{k})}{\chi_T(k)} + \int d\mathbf{k}\,\frac{\mathbf{P}_L(\mathbf{k})\cdot\mathbf{P}_L(-\mathbf{k})}{\chi_L(k)}\right]. \end{aligned} \tag{51}$$

(beware of the definition of χ_L, with or without a 4π factor [79, 81]).

At the end, one can gather all the above equations, including eqs. 13,41,51 to get the following functional for a dipolar fluid, defined in terms of the density and dielectric susceptibilities

$$\begin{aligned} \mathcal{F}_{id}[n, \mathbf{P}] &= k_BT\int d\mathbf{r}d\boldsymbol{\omega}\left[\rho(\mathbf{r},\boldsymbol{\omega})\ln\left(\frac{4\pi\rho(\mathbf{r},\boldsymbol{\omega})}{n_0}\right) - \rho(\mathbf{r},\boldsymbol{\omega}) + \frac{n_0}{4\pi}\right] \\ &+ \int d\mathbf{r}\,\Phi_{LJ}(\mathbf{r})\,n(\mathbf{r}) - \frac{k_BT}{2n_0}\int d\mathbf{r}\,\Delta n(\mathbf{r})^2 \\ &+ \frac{k_BT}{2}\int d\mathbf{r}_1 d\mathbf{r}_2\,\chi_n^{-1}(r_{12})\,\Delta\rho(\mathbf{r}_1)\Delta\rho(\mathbf{r}_2) \\ &- \int d\mathbf{r}\,\mathbf{P}(\mathbf{r})\cdot\mathbf{E}_q(\mathbf{r}) - \frac{3k_BT}{n_0\mu^2}\int d\mathbf{r}\,\mathbf{P}(\mathbf{r})^2 \\ &+ \frac{1}{8\pi\epsilon_0}\int d\mathbf{r}_1 d\mathbf{r}_2\,\chi_T^{-1}(r_{12})\,\mathbf{P}_T(\mathbf{r}_1)\cdot\mathbf{P}_T(\mathbf{r}_2) \\ &+ \frac{1}{8\pi\epsilon_0}\int d\mathbf{r}_1 d\mathbf{r}_2\,\chi_L^{-1}(r_{12})\,\mathbf{P}_L(\mathbf{r}_1)\cdot\mathbf{P}_L(\mathbf{r}_2) + \mathcal{F}_B[n, \mathbf{P}]. \end{aligned} \tag{52}$$

The ideal part can also be taken as in eq. 43 so that the whole functional can be minimized with respect to $n(\mathbf{r})$ and $\mathbf{P}(\mathbf{r})$. The bridge term can be neglected (HNC approximation) or approximated as a functional of $n(\mathbf{r})$ only, $\mathcal{F}_B[n]$, for example using the hard-sphere bridge functional of Section 2.2

As a short illustration, Fig. 4a shows the accuracy of the MDFT approach (within the HNC approximation) for the microscopic structure of the Stock-mayer solvent around neutral and charged spherical solutes [37, 38, 63]. The MDFT results are compared to direct MD simulations of the solute embedded in the solvent. They do appear very satisfactory and account accurately for the shape of the peaks and their variation with charge and size (despite a slight overestimation of the first peak height for the neutral solute). Fig. 4b illustrates the case of a multisite polar molecule (here a three-site model of the acetonitrile molecule) with similar conclusions. An application to a more complex molecular system, namely the three-dimensional solvation structure close to an atomistically resolved clay, is illustrated in Fig. 5 and described further in Ref. [66].
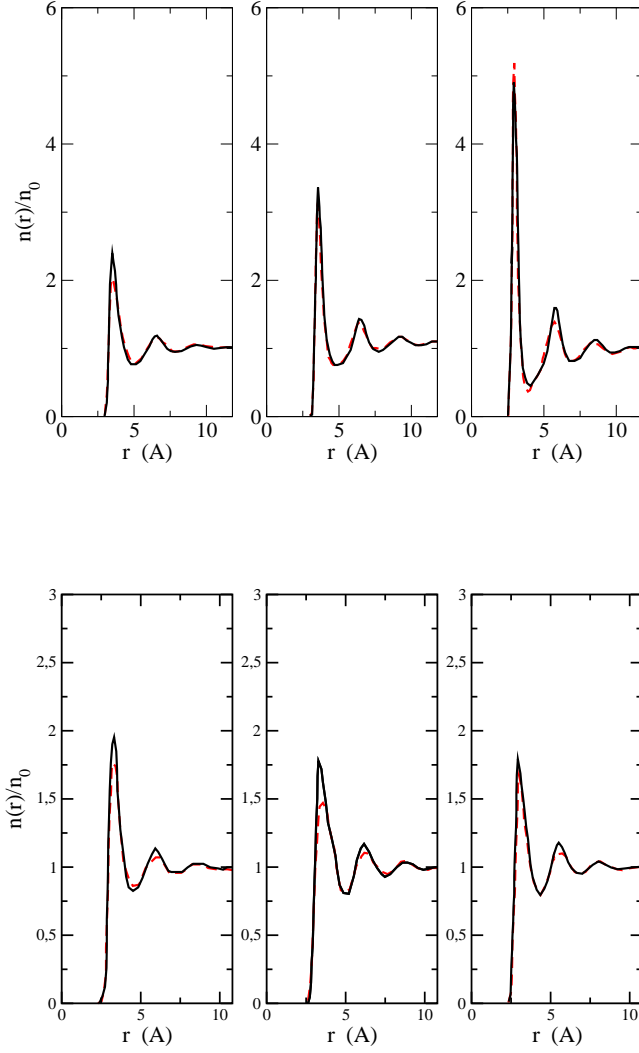
Figure 4: Top: Reduced density of the Stockmayer solvent around various solutes. MDFT results (solid black lines) are compared to MD simulation results (dashed red lines). From left to right: CH_4, Cl^-, K^+. Bottom: Same than for the various sites of an acetonitrile molecule dissolved in the Stockmayer solvent. From left to right: CH_3, C, N.
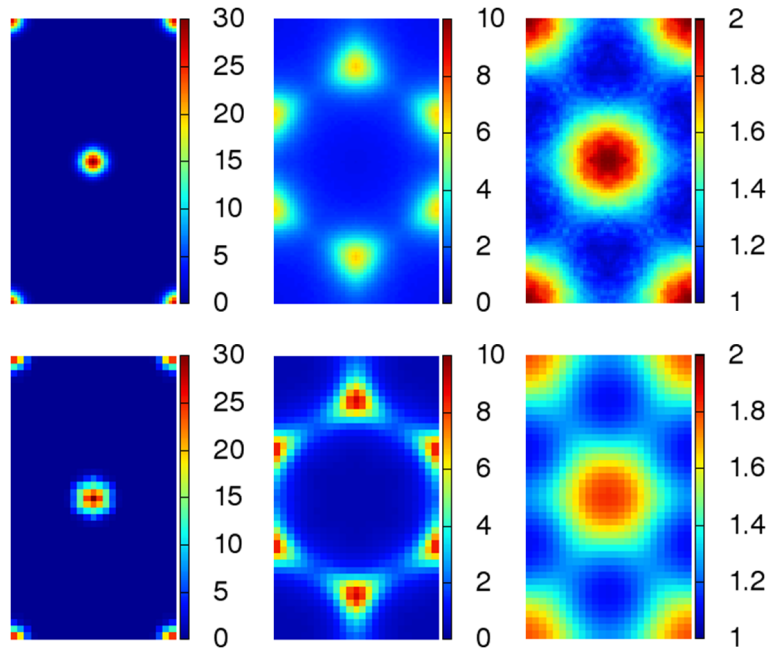
Figure 5: Two-dimensional maps of the solvent number density $n(\mathbf{r})/n_0$ in three different planes close to a neutral clay surface, as calculated by molecular dynamics (top) and HRF-MDFT (bottom). Those planes correspond to a prepeak (left), the first maximum (center) and second maximum (right) of the out-of plane mean solvent density. See Ref. [66]
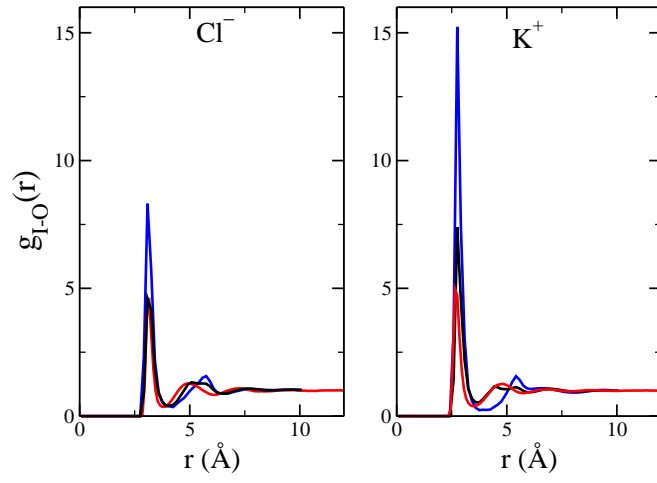
Figure 6: Ion-oxygen pair distribution functions for chloride and potassium ions in SPC/E water computed by MD (red lines) or MDFT without (blue lines) or with the three body term described in Ref. [68] (black lines)
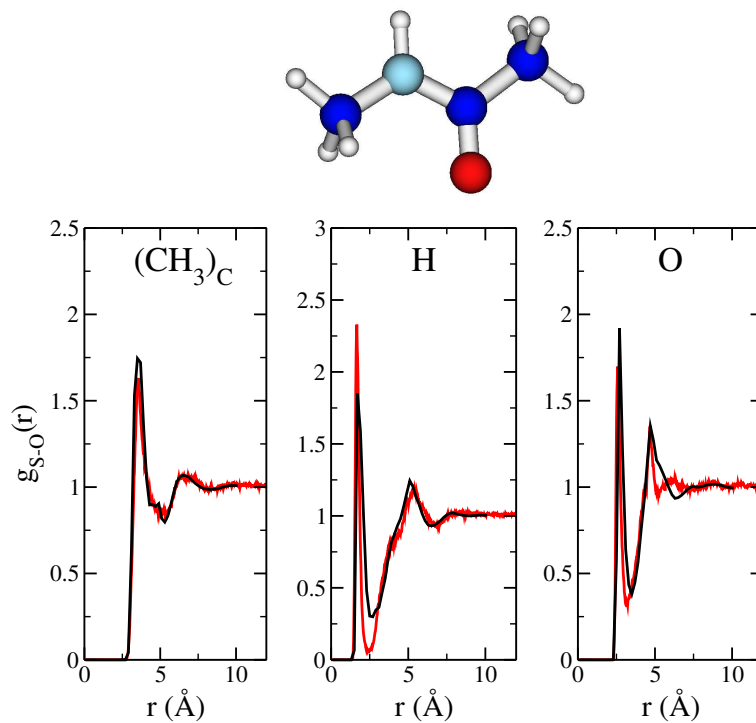
Figure 7: A selection of solute site-oxygen pair distribution functions for the n-methyl-acetamide molecule $CH_3NHCOCH_3$ (shown on top) computed by MD (red lines) or MDFT (black lines), including the three-body term described in Ref. [68] .

3.3 Extension to water and arbitrary molecular solvents

Water is a special case, certainly by its very subtle physics, but also for the fact that the most popular molecular models fall in the category of simple point charge models with a single Lennard-Jones center (usually centered on the oxygen atom) and distributed point charges. In that case, it was shown recently that the functional just displayed in eq. 52 (with the linear orientation vector $\boldsymbol{\omega}$ substituted by the three-angle orientation ω, and 4π by $8\pi^2$) is perfectly applicable if the dipolar polarization $\mathbf{P}(\mathbf{r})$ is replaced by a multipolar polarization vector, accounting for the full charge distribution of the water molecule, and defined in k-space by

$$\mathbf{P}(\mathbf{k}) = \int d\omega \boldsymbol{\mu}(\mathbf{k},\omega)\rho(\mathbf{k},\omega) \tag{53}$$

with

$$\boldsymbol{\mu}(\mathbf{k},\omega) = -i\sum_m q_m \frac{\mathbf{s}_m(\omega)}{\mathbf{k}\cdot\mathbf{s}_m(\omega)}\left(e^{i\,\mathbf{k}\cdot\mathbf{s}_m(\omega)}-1\right) \tag{54}$$

$$= \boldsymbol{\mu}(\omega) + \frac{i}{2}\sum_m q_m\left(\mathbf{k}\cdot\mathbf{s}_m(\omega)\right)\mathbf{s}_m(\omega) + ..., \tag{55}$$

being defined as the polarization, of a single molecule located at the origin. $\mathbf{s}_m(\Omega)$ designates the location of the mth atomic site for a given orientation ω. It reduces to the usual molecular dipole $\boldsymbol{\mu}(\omega) = \sum_m q_m\,\mathbf{s}_m(\omega)$ at dominant order in $\mathbf{k}$. The multipolar dielectric susceptibilities $\chi_L(k)$ and $\chi_T(k)$ entering in eq. 52 can be either computed from MD simulations of the pure liquid, according to the procedure in Refs [81,82], or inferred from experiments.

Although giving already sensible results for rather complex systems [69], it was shown in that the HNC approximation $\mathcal{F}_B = 0$ turns unfortunately short for describing the solvation of hydrophobes [65,67], as well as that of molecular solutes giving raise to strong H-bonds [68]. Three-body corrections, including a spherical HS bridge, or a three-body term re-enforcing tetrahedral order, have to be added to give correct solvation structure and thermodynamics. This is illustrated in Fig. 6 for the hydration structure around monovalent ions. Fig. 7 shows the water structure obtained by MDFT around a N-methyl-acetamide molecule (the prototype for a NH-CO peptide motif), including the three-body correction term in the functional. [68]

For a general solvent with more complex geometry, and described by more than one Lennard-Jones center, the full angular-dependent functional of Sec. 3.1 has to be adopted, and the necessary input remains the full angular-dependent direct correlation function $c(\mathbf{r}_{12},\boldsymbol{\omega}_1,\boldsymbol{\omega}_2)$. Remaining in the HNC approximation, this formulation was applied with some success to the study of charge transfer processes in acetonitrile [64].

The MDFT approach is still under current development, as are related site-DFT approaches [71], for practical applications such as the systematic prediction of solvation free energies [70]. Classical density functional theories are expected to provide soon an alternative to the 3D-RISM approach, which is nowadays

becoming quite popular for applications in biological and material sciences –
despite some intrinsic theoretical limitations that specialists are aware of.

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